REMARKS

The examiner maintains the obviousness rejections, as well as the rationale asserted. It is again noted that these rejections are untenable under clear US law.

The examiner alleges that applicants have not addressed the examiner's position on Licha et al. (page 9 of the office action, paragraph 28). This is not true. See the third paragraph on page 6 of the last response, for instance. In any event, it is not sufficient for a rejection under 35 USC 103 to simply note that a particular reference (Licha et al.) discloses a very broad class of compounds all of which are presumed effective for a certain use. As applicants have maintained all along, and as is clear under US law, it is irrelevant whether the infinite compound scope of Licha et al. is all useful for Licha's use. Thus, it is not in any way necessary for applicants to provide a reason to expect that any of Licha's compounds would not be effective for in vivo imaging, as the examiner alleges in paragraph 28.

The proper test under KSR International Company v. Teleflex Inc., 1550 US__, 82 USPQ2d 1385 (2007) is whether there is motivation to select the compounds claimed in this application from among all of those disclosed as possible in Licha et al. The latter is completely bereft of any such motivation as applicants have detailed of record in the last response, e.g., on page 6.

In addition, the Federal Circuit has specifically addressed the issue of whether, simply because a reference discloses a very broad genus of compounds for a certain purpose, it is obvious to use all of such compounds for such use. The court has held that there is no such rule, contrary to the examiner's continued statements to the contrary. See, e.g., *In re Jones, 958 F.2d 347 (Fed.Cir. 1992).* There the court stated: "We decline to extract from *Merck* the rule that the Solicitor appears to suggest - that regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it. "Rather, as in *KSR*, Jones stated that it is incumbent upon the PTO to explain why a skilled worker would be motivated to select a particular claimed compound or subgenus from among the very broad prior art genus in order to arrive at the claimed invention. The examiner has consistently failed to supply any such reasons. The reason is simple: there is no basis in Licha et al. to select the claimed compounds for the claimed use. Thus, this rejection is untenable.

The same is true of the combination of Licha et al. with Ohno et al. The examiner alleges that the motivation to combine these references is derived from the fact that Ohno describes its particular compounds as "dyes." See page 13 of the office action. But this fact must be completely irrelevant to the Licha disclosure because Licha itself clearly describes that all of its claimed infinite scope of compounds are dyes. Note the definition of F in the portions of the Licha disclosure relied on by the examiner which indicates that "F represents a dye..." Since all Licha's structures relied on by the examiner are already disclosed as dyes by Licha et al., there is no logic to the examiner's assertion that the fact that Ohno discloses a subset as dyes would lead a skilled worker to pick such subset.

Rather, in order for Ohno to be combinable with Licha, there must be something in Ohno which would indicate to a skilled worker that there is a particular reason to select Ohno's compounds for Licha's use. But, as already explained in detail in the last response, Ohno's use relates to one which is not relevant to Licha's in vivo imaging use. Rather, Ohno's field is the field of photography using silver photosensitive material. The examiner has consistently failed to explain on the record why a skilled worker would learn from Ohno's use of dyes in a certain layer in a photographic film, a reason to utilize such dyes in the completely different methodology of Licha involving in vivo imaging. There is no connection of record. Thus, the examiner has failed to satisfy the legal test for the combinability of references. He has failed to explain on the record why a skilled worker would select Ohno's photographic layer dyes for use in Licha's method. Thus, there is nothing on the record which establishes a motivation to combine the references or a motivation to select from the infinite scope of Licha, those compounds recited in the claims of this application.

Accordingly, both prior art rejections are untenable and should be withdrawn.

Applicants will attend to the double patenting rejections as soon as an allowable scope of subject matter is otherwise determined in this application. It would be premature to file a terminal disclaimer or assess the legitimacy of the double patenting rejection until such allowable scope is determined.

Even if Licha alone or the combination of Licha and Ohno had established a prima facie case of obviousness, the data on record is effective to rebut it, not that this is needed.

It has been established of record that the LD_{50} is for the claimed sodium salts are

unexpectedly higher than the LD_{50} values for the corresponding potassium salts. The examiner does not seem to dispute this point. Rather, it is his position that these data are not significant.

Basically, the examiner notes that an example of this application uses a particular dose and that this dose is lower than that of the LD_{50} values involved. It is the examiner's position that the differential between the particular dose used in the example and the LD_{50} values for all of the sodium and potassium salts is so large, that any differences among the LD_{50} values themselves are not significant. This is incorrect. LD_{50} value differences are significant in pharmaceutical design under the circumstances of this case.

The examiner, in part, supports his position in the last office action with reference to figure 3-3 of Goodman. Firstly, the latter figure represents curves generated for a particular sedative-hypnotic and in no way establishes any general principles, as far as the undersigned can determine. In any event, figure 3-3 demonstrates that the pharmaceutical industry in general not only looks at LD_{50} and ED_{50}, but also parameters such as LD_1 and ED_{99}. The attached internet excerpts show that the ratio of LD_1 to ED_{99} is called the "certain safety factor." This is the ratio of the lethal dose to 1% of the population to the effective dose to 99% of the population. This clearly shows that the pharmaceutical industry is not only concerned with the particular normal dose which might be given for a certain drug, but also the full range of dosage effects for a drug, including much higher and much lower doses. For the figure relied on by the examiner from Goodman, there is not "substantially no overlap," as alleged. Rather, there is a significant dose overlap between LD_1 and ED_{99}. In other words, at doses up to those effective in 99% of the population, deaths clearly will occur since the ED_1 dose is lower.

Certainly, it is not the examiner's position that it is irrelevant that some people might die in the use of a drug. Rather, any factor that would indicate that a drug could cause fewer deaths within the effective dose range is always an important consideration. Thus, maximizing LD_{50} is always a desired end result, irrespective of the dose administered in a generic case. Whereas an LD_{50} very much higher than a particular dose used (or an ED_{50}) may give a drug company comfort, an LD_{50} even higher, would give a drug company even more comfort. In other words, it is always a desirable outcome to those of ordinary skill in the field to lessen the toxicity and possible side effects of a drug, even if this might only affect a single individual in the world. Thus, when considering only LD_{50}, higher is always better. This is clearly reflected in the certain

safety factor parameter where very low LDs and very high EDs are considered relevant.

The point with the foregoing is that patent applications are filed at early stages of drug discovery. Consequently, the Federal Circuit has consistently held that what is relevant to FDA may not be particularly relevant to patentability. *In re Brana, 51 F.3d 1560 (Fed.Cir. 1995).* For example, insofar as recommended dosage ranges are concerned at the FDA, these have to do with clinical data which are almost never involved when a patent application is filed at early stages of development. In any event, as shown above, LD_{50} values per se are always relevant irrespective of any contemplated effective dosage range. Whereas it is true that the data calculated in applicant's response are not a true therapeutic index, this is clearly indicated in the table on page 9 where the definition of TI is provided. These data were simply calculated in an effort to demonstrate the relevance of applicant's argument to the examiner's position which is based on a particular value of dosage and not ED_{50}.

It is not applicant's position that the particular parameter of therapeutic index establishes unexpected properties. Rather, it is applicant's position that the increased LD_{50} values per se, given the realities of drug development, establish unexpected results for the claimed subject matter in and of themselves.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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